Disorders of Immunity and Inflammation

Hypersensitivity

Exaggerated Immune Response

Hypersensitivity Types

- Allergy
  - Exogenous, non-human antigen
- Isoimmunity (alloimmunity)
  - Exogenous, human antigen
- Autoimmunity
  - Endogenous antigen

Hypersensitivity Mechanisms

- Type I: IgE mediated
- Type II: Tissue specific
- Type III: Immune complex mediated
- Type IV: Cell mediated

Type I

- Immediate hypersensitivity
- IgE mediated
- Exogenous antigen

Most (but not all) Allergies

Type I: Mechanism

- Repeated antigen exposure causes increased IgE production
- IgE binds to mast cells
- Sensitization occurs

Type I: Mechanism

- Antigen binds to IgE on mast cell membrane
- Mast cell releases histamine, chemotaxic factors
- Inflammatory response occurs

Type I: Signs/Symptoms

- Clinical signs, symptoms = response to histamine release
- GI, skin, respiratory system
  - High mast cells numbers
  - Most sensitive

Type I: Signs/Symptoms

- Histamine effects
  - Vasodilatation
  - Increased capillary permeability
  - Non-vascular smooth muscle spasm

Type I: Signs/Symptoms

- Skin: flushing, itching, edema, urticaria, hives
- Respiratory: bronchospasm, laryngospasm, laryngeal edema
- Cardiovascular: tachycardia, hypotension
- GI: nausea, vomiting, cramping, diarrhea

Type I: Atopia

- “Allergy prone” individuals
- Genetic predisposition
- More IgE
- More mast cell receptors for antibodies than normal

Type I: Anaphylaxis

- Severe, generalized Type I reaction
- Life-threatening
  - Loss of airway
  - Ventilatory failure
  - Hypoperfusion

Type II

- Tissue specific
- Reaction to tissue-specific antigens
- Causes target cell destruction, dysfunction
- Exogenous or endogenous antigen

Type II

- Most commonly affected cells
  - Red blood cells
  - Thyroid cells

Type II: Mechanisms

- Antibody binds to cell membrane, triggers compliment-mediated lysis
- Examples
  - Reaction to transfused blood
  - Hemolytic disease of newborn

Type II: Mechanisms

- Antibodies promote target cell clearance by macrophages

Type II: Mechanisms

- Antibodies bind to target cells and cytotoxic T-cells
- Trigger release of toxins to destroy target cells

Type II: Mechanisms

- Antibody binds to cell membrane, causes alterations in target cell function
- Example: Graves' disease
  - Antibody binds to thyroid cell membrane
  - Mimics Thyroid Stimulating Hormone action
  - Causes production of excessive amounts of thyroid hormone
  - Results in common form of hyperthyroidism

Type III

- Mediated by antigen/ antibody complex deposition in tissues
- Exogenous or endogenous antigen

Type III: Mechanism

- Ag-Ab complex deposited in tissues
- Especially sensitive tissues are blood vessels, GI, respiratory system
- Causes complement activation, increased neutrophil activity
- Neutrophils have trouble digesting complexes, release lysosomes causing damage

Type III

- Immune complex quantity varies over time
- Symptomatic periods alternate with periods of remission

Type III: Serum Sickness

- Repeated intravenous antigen injections
- Immune complexes deposited in tissues
- Fever, rash, pain, lymphadenopathy

Type III: Raynaud's Phenomenon

- Temperature governs immune complex deposition in peripheral circulation
- Exposure to cold causes redness, pain of fingers, toes followed by numbness, cyanosis, gangrene

Type III: Arthus Reaction

- Occurs after repeated LOCAL exposure to exogenous antigen
- Immune complexes in vessel walls
- Examples
  - Celiac disease from wheat protein
  - Hemorrhagic alveolitis from moldy hay inhalation

Type IV

- Delayed
- Mediated by Td (lymphokine-producing) or Tc (cytotoxic) cells
- No antibody involved

Type IV

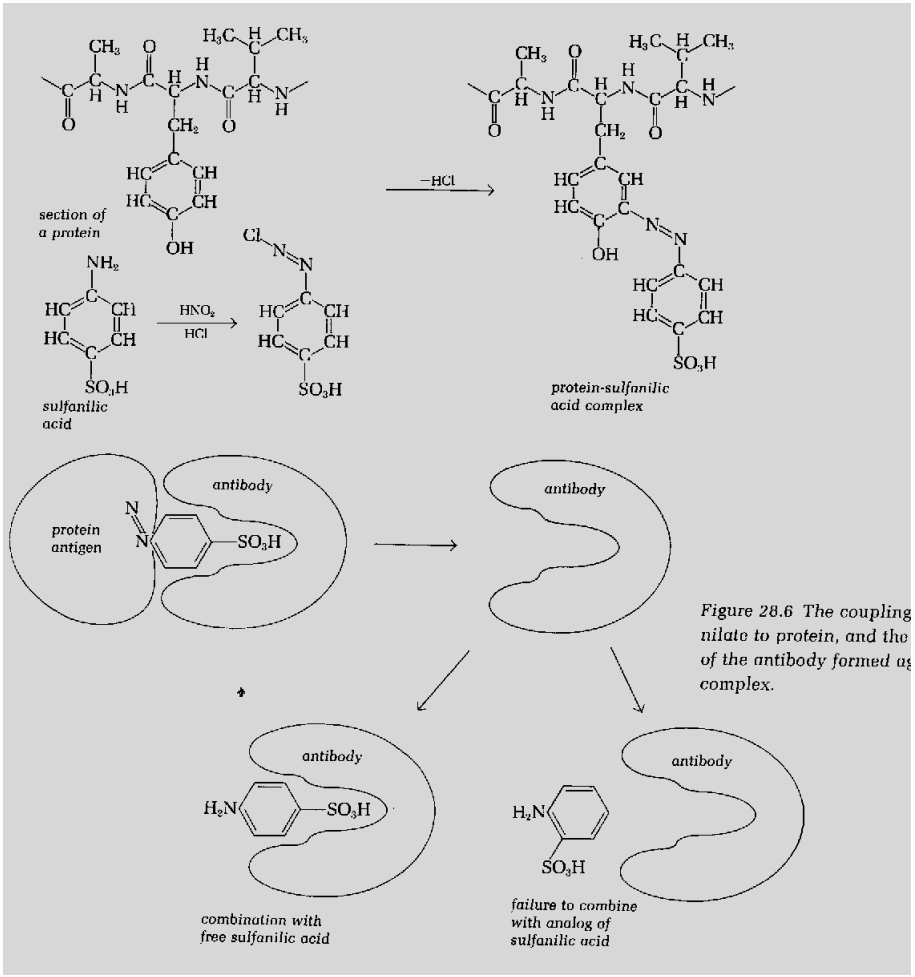
- Examples
  - Graft rejection
  - Contact allergic reactions (poison ivy)

Hypersensitivity Targets

- Allergins
  - Pollen (hay fever)
  - Drug reactions
  - Foods

Hypersensitivity Targets

- Neoantigens
  - Hapten binds to protein molecule
  - Changes its antigenicity
  - Causes it to become an allergen



Hypersensitivity Targets

- Autoantigens
  - Sequestered cells (cornea, testes)
  - Foreign antigen triggered (infection)
  - Suppressor T-cell malfunction
  - Genetic causes

Hypersensitivity Targets

- Isoantigens
  - Tissue grafts, transplants
  - Rh negative sensitivity

Autoimmune Disease

Clinical disorder produced by immune response to normal tissue component of patient's body

Graves' Disease

- Antibody stimulates thyroid hormone over production
- Produces hyperthyroidism
- Antibody, disease can be passed through placenta

Rheumatoid Arthritis

- Antibody reaction to collagen in joints
- Causes inflammation, destruction of joints

Myasthenia Gravis

- Antibodies destroy acetylcholine receptors on skeletal muscle
- Produce episodes of severe weakness
- Antibodies can cross placenta, affect newborn

Immune Thrombocytopenic Purpura

- Antibodies destroy platelets
- Produces clotting disorders, hemorrhaging
- Antibodies can cross placenta, affect newborn

Isoimmune Neutropenia

- Antibodies attack, destroy neutrophils
- Can cross placenta, affect newborn

Other Autoimmune Diseases

- Type I diabetes mellitus
- Primary myxedema
- Rheumatic fever
- Crohn’s disease
- Ulcerative colitis
- Systemic Lupus Erythematosis (SLE)

Systemic Lupus Erythematosis (SLE)

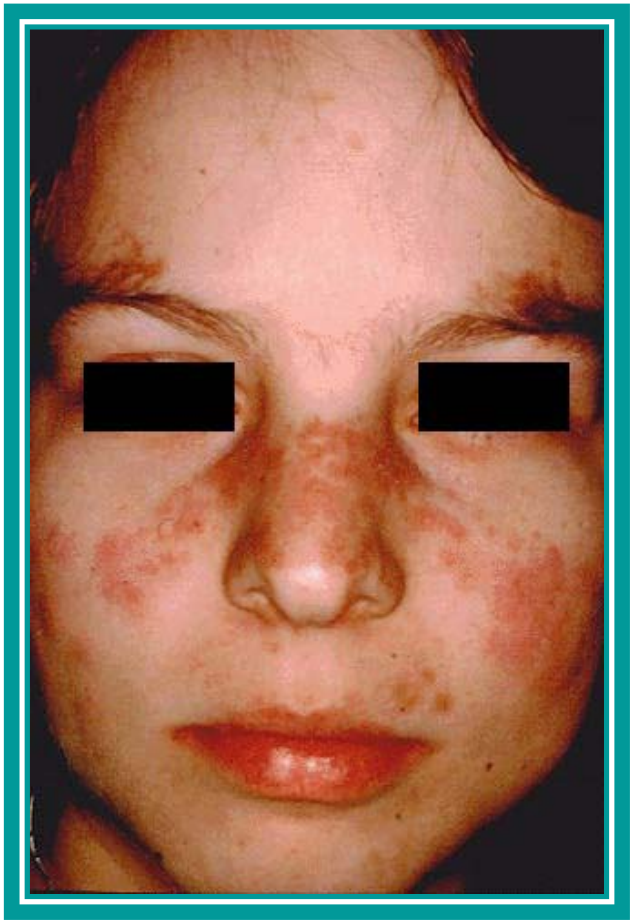
- Chronic, multi-system auto-immune disease
- Highest incidence
  - Women, 20-40 years of age
  - Black, Hispanic women
- Mortality after diagnosis averages 5% per year

Systemic Lupus Erythematosis (SLE)

- Antibody against nucleic acid components (ANA, anti-nuclear antibody)
- Immune complex precipitates in tissues, causes widespread destruction
- Especially affected are renal system, blood vessels, heart

Systemic Lupus Erythematosis (SLE)

- Signs/Symptoms
  - Facial rash/skin rash triggered by sunlight exposure
  - Oral/nasopharyngeal ulcers
  - Fever
  - Arthritis



Systemic Lupus Erythematosis (SLE)

- Signs/Symptoms
  - Serositis (pleurisy, pericarditis)
  - Renal injury/failure
  - CNS involvement with seizures/psychosis
  - Peripheral vasculitis/gangrene
  - Hemolytic anemia

Systemic Lupus Erythematosis (SLE)

- Chronic management
  - Anti-inflammatory drugs
    - Aspirin
    - Ibuprofen
    - Corticosteroids
  - Avoidance of emotional stress, physical fatigue, excessive sun exposure

Disorders of Immunity

Immunodeficiency Diseases

Immunodeficiency Disease

- Patient unable to fight off infection
- Hallmarks
  - Repeated infections
  - Opportunistic infections

Immunodeficiency Disease

- Most are defects in T cells or B cells
  - T cells, macrophage defects = fungal, viral infections
  - B cells, complement defects = bacterial infections

Immunodeficiency Disease

- Congenital
- Acquired

Congenital

- B-cell Deficiency
- IgA Deficiency
- DiGeorge's Syndrome
- Severe Combined Immunodeficiency

B Cell Deficiency

- Agammaglobulinemia
- Hypogammaglobulinemia

IgA Deficiency

- Most common immune deficiency disorder
- Genetic condition
- Failure of IgA synthesis
- Patient has repeated, recurrent sinus, lung, GI infections

DiGeorge's Syndrome

- Thymic hypoplasia
- Severe decrease in T-cell production, function
- Defects of face, ears, heart

Severe Combined Immunodeficiency

- Thymus development arrested at ~6-8 weeks gestation.
- Deficiency, defective maturation of stem cells that produce B and T cells
- Little to no antibody production

SCID

- Two types
  - Autosomal recessive
  - X-linked disease recessive

SCID

- Recurrent, frequently overwhelming infections
- Particularly respiratory, gastrointestinal
- Most die in first few years of life, usually by one year of age
- Death usually due to opportunistic infection

Acquired

- Nutritional deficiency
- Iatrogenic (drugs, radiation)
- Trauma (prolonged hypoperfusion)
- Stress
- Infection (HIV)

Immune Deficiency Therapies

- B-cell deficiency: Gamma globulin
- SCID: Bone marrow transplants, enzyme replacement
- DiGeorge's Syndrome: Fetal thymus transplants
- Gene therapy